APPENDIX I

132 DECLARATION OF NATHANIEL JULIUS MONCK

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

Attorney Docket No. 040283-0211

In re patent application of
David Reginald ADAMS et al.
Serial No. 10/685,799
Filed: 10/16/ 2003
For: PYRAZINO (AZA)INDOLE DERIVATIVES

Group Art Unit: 1624
Examiner: V. Balasubramanian

DECLARATION UNDER 37 CFR § 1.132 OF NATHANIEL JULIUS MONCK

Commissioner for Patents
Washington, D.C. 20231

Sir:

I, Nathaniel Julius Monck, the undersigned, a citizen of Great Britain and a resident of Sunningdale, United Kingdom, do hereby declare that:

1. I am the Senior Scientist responsible for the 5HT2C project and I am familiar with the invention described in the above-identified patent application entitled "PYRAZINO (AZA)INDOLE DERIVATIVES" which was given United States Serial No. 10/685,799.

2. I graduated as a Bachelor of Science from University of Bristol in 1990, and completed a Doctoral Degree from Imperial College, London University in 1993.

3. Since August 1996, I have been employed by VERNALIS RESEARCH LIMITED, assignee of the above-identified application, where I have been engaged in research and development of drugs useful in the treatment of CNS disorders.

4. I attach my Curriculum Vitae.

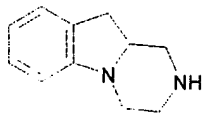
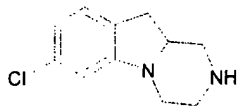
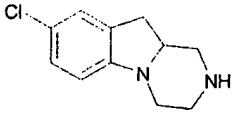
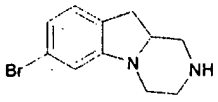
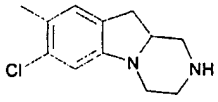
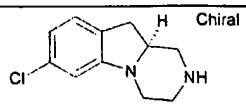
5.1 It is my understanding that the Examiner considers the subject-matter claimed in the above-identified application to be obvious over Mokrosz *et al* (Med. Chem. Res. 3: 240-248, 1993).

5.2 Compounds (6) and (7) in the Mokrosz prior art differ from the presently claimed compounds in that the phenyl ring is unsubstituted. The presently claimed

compounds require that *"either at least one of R_5 and R_6 is selected from chlorine, fluorine, haloalkyl and bromine, or R_5 is selected from halogen, haloalkyl and alkylthio"*. It is my understanding that the Examiner considers these substituted compounds to be obvious. However, we have been able to show an unexpected advantage of the presently claimed compounds.

5.3 The comparative data are set out in Tables 1 and 2 below. Table 1 shows the weak efficacy of the unsubstituted compounds of Mokrosz. In contrast, all the presently-claimed substituted compounds have EC50 values from 7 to 300-fold lower than the unsubstituted examples of the prior art. The presently claimed compounds therefore possess greater agonist potency than those of Mokrosz. The superiority of the presently claimed compounds could not have been predicted, and we believe therefore that the claimed subject-matter should not be considered obvious.

Table 1

Compound	Structure	EC50 (5-HT_{2C})
Prior Art Example		1085 nM
Example 1		18
Example 2		162
Example 4		13
Example 5		20
Example 7		161

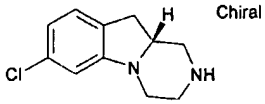
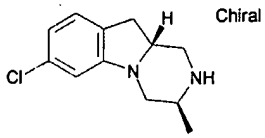
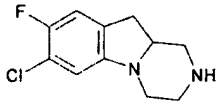
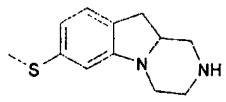
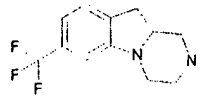
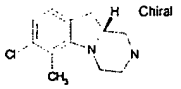
Example 8		3
Example 11		58
Example 12		22
Example 13		86

Table 2

Structure	R group exemplified	EC50 5HT2C / nM
	R_5 = trifluoromethyl	102
	R_4 = methyl, R_5 = chloro	116

6. I further declare that all statements herein of my own knowledge are true and that all statements made on information and belief are believed to be true; and further that these statements were made with the knowledge that willful false statements and the like so made are punishable by fine or imprisonment, or both, under Section 1001 of Title 18 of the United States Code, and that such willful false statements may jeopardize the validity of the application or any patent issued thereon.

Date: 17th March 2006

Nathaniel Julius Monck

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

APPENDIX II

CURRICULUM VITAE OF NATHANIEL JULIUS MONCK

Nathaniel Julius Thomas Monck

10 Park Crescent, Sunningdale, Berkshire, SL5 0AX, UK.

Date of Birth: 16 July 1968

Professional Experience:

Aug 1996-present date	**Vernalis Research Ltd**, Winnersh Triangle. Principal Scientist, Chemistry Dept. Anxiety Project Leader (chemistry) 1997-2001 Sodium Channel Project Leader (chemistry) 2001-present date
Feb 1996-Aug 1996	**SmithKline Beecham**, Harlow. Industrial post-doctoral position. Synthesis of conformationally restricted unnatural amino-acids and incorporation into peptide mimetic libraries via combinatorial chemistry.
Feb 1995-Nov 1995	**The Australian National University**, Canberra, ACT. Post-Doctoral Research Fellow Research Advisor: Professor Lewis N. Mander, FRS Studies towards the total synthesis of gibberellic acid GA_{103}, the total synthesis of Harringtonolide and the partial synthesis of 7β-hydroxy-kaur-16-en-19-oic acid.
Jan 1994-Jan 1995	**The Ohio State University**, Columbus, Ohio. Post-Doctoral Research Fellow Research Advisor: Professor Leo A. Paquette Studies towards the total synthesis of Jatrophatrione.
Oct 1990-Dec 1993	**Imperial College**, University of London. Research Fellow; Research Advisor: Professor Steven V. Ley, FRS Development of new synthetic methods for the total synthesis of Milbemycin α_1 and Nemadectin β utilising relay studies of Nemadectin γ. Undergraduate Teaching Assistant; supervision and demonstration of laboratory experiments.
Oct 1992-Dec 1992	**Rhône-Poulenc-Rorer**, Dagenham. Research Fellow; Research Advisor: Dr Michael Ashton CASE award industrial placement.
Jul 1989-Aug 1989	**Institute of Child Health/Great Ormond Street Hospital**, London. Research Assistant; Research Advisor: P. Bird. Studies towards the development of HPLC methods for the analysis of samples from neofibroblastomer patients.

Awards/Honours:

1997-1998	MRSC CChem awarded as result of Structured Assessment.
1990-1993	CASE Award from Rhône-Poulenc-Rorer.

Courses:

Dec 1998	Introduction to Molecular Modelling, including the use of Legion, Selector, Flexidock and Gasp operations; Tripos Inc., Milton Keynes
July 1997	Medicinal Chemistry Residential Course: An introduction to the pharmaceutical industry. RSC, Canterbury.

Education:

1990-1993	Imperial College, University of London PhD, DIC, Synthetic Organic Chemistry Research Advisor: Professor Steven V. Ley, FRS Dissertation: Studies towards the Total Synthesis of the Milbemycins.
1987-1990	University of Bristol, Bachelor of Science (Hons), Chemistry, First class. Final year project supervisor: Dr Thomas V. Lee Dissertation: The Use of Enzymes in Organic Media.
1979-1986	Acland Burghley Comprehensive School, London A-levels: Chemistry (A), Mathematics (B), Physics (A) O-levels: French, History, Geography, Music, Chemistry, Physics, Mathematics, Advanced Mathematics, English Literature, English Language.

Bibliographic Information

Cizolirtine(Laboratorios Dr Esteve). Monck, Nathaniel. Vernalis Research Ltd, Wokingham, UK. Current Opinion in Investigational Drugs (PharmaPress Ltd.) (2001), 2(9), 1269-1272.

Preparation of indole derivatives as agonists or antagonists of a 5-HT receptor, particularly a 5-HT2C receptor. Bentley, Jonathan Mark; Roffey, Jonathan Richard Anthony; Davidson, James Edward Paul; Mansell, Howard Langham; Hamlyn, Richard John; Cliffe, Ian Anthony; Adams, David Reginald; Monck, Nathaniel Julius. (Vernalis Research Limited, UK). PCT Int. Appl. (2001), 67 pp. CODEN: PIXXD2 WO 0112603 A1.

Preparation of azetidine carboxamides for the treatment of CNS disorders. Snape, Mike Frederick; Fletcher, Allan; Stanhope, Kelly Jean; Monck, Nathaniel Julius. (Vernalis Research Limited, UK). PCT Int. Appl. (2001), 39 pp. CODEN: PIXXD2 WO 0107043 A1 20010201.

Preparation of azetidine-1-carboxamide derivatives as neuroprotectants. Snape, Mike; Monck, Nathaniel Julius; Fletcher, Allan; Stanhope, Kelly Jean; Mansell, Howard Langham; Nelson, Alan John. (Vernalis Research Limited, UK). PCT Int. Appl. (2001), 31 pp. CODEN: PIXXD2 WO 0107023 A2 20010201.

2-adamantanemethanamine compounds for treating abnormalities in glutamatergic neurotransmission, and preparation thereof. Gillespie, Roger John; Monck, Nathaniel Julius Thomas; Bird, Andrew James; Ward, Simon Edward. (Vernalis Research Limited, UK). PCT Int. Appl. (2000), 35 pp. CODEN: PIXXD2 WO 0044371 A1 20000803.

3,5-Disubstituted-4-hydroxyphenyls Linked to 3-Hydroxy-2-methyl-4(1H)-pyridinone: Potent Inhibitors of Lipid Peroxidation and Cell Toxicity. Bebbington, David; Monck, Nathaniel J. T.; Gaur, Suneel; Palmer, Alan M.; Benwell, Karen; Harvey, Victoria; Malcolm, Craig S.; Porter, Richard H. P. Departments of Chemistry and Molecular Pharmacology, Cerebrus, Winnersh Wokingham, UK. Journal of Medicinal Chemistry (2000), 43(15), 2779-2782.

Dual-mechanism antioxidants: Novel neuroprotective compounds--II. Bebbington, David; Gaur, Suneel; Dawson, Claire E.; Monck, Nathaniel J. T.; Palmer, Alan M.; Harvey, Victoria; Malcolm, Craig S.; Porter, Richard H. P. Department of Chemistry, Cerebrus, Wokingham, UK. Book of Abstracts, 219th ACS National Meeting, San Francisco, CA, March 26-30, 2000 (2000), MEDI-093.

Synergistic dual-mechanism antioxidants: Novel neuroprotective compounds--I. Bebbington, David; Monck, Nathaniel J. T.; Gaur, Suneel; Palmer, Alan M.; Benwell, Karen R.; Harvey, Victoria; Malcolm, Craig S.; Porter, Richard H. P. Department of Chemistry, Cerebrus, Wokingham, UK. Book of Abstracts, 219th ACS National Meeting, San Francisco, CA, March 26-30, 2000 (2000), MEDI-092.

Preparation of indolinealkylamine derivatives as 5-HT2B and/or 5-HT2C receptor ligands. Adams, David Reginald; Bentley, Jonathan Mark; Roffey, Jonathan Richard Anthony; Hamlyn, Richard John; Gaur, Suneel; Duncton, Matthew Alexander James; Bebbington, David; Monck, Nathaniel Julius; Dawson, Claire Elizabeth; Pratt, Robert Mark; George, Ashley Roger. (Cerebrus Pharmaceuticals Limited, UK; et al.). PCT Int. Appl. (2000), 81 pp. CODEN: PIXXD2 WO 0012475 A1 20000309.

Preparation of 2-adamantanecarboximidamides NMDA receptor antagonists. Monck, Nathaniel Julius Thomas; Gillespie, Roger John; Bird, Andrew James. (Cerebrus Limited, UK). PCT Int. Appl. (1999), 34 pp. CODEN: PIXXD2 WO 9938841 A1 19990805.

Azetidinecarboxamide derivatives for the treatment of CNS disorders. Adams, David Reginald; Cliffe, Ian Anthony; Mansell, Howard Langham; Monck, Nathaniel Julius. (Cerebrus Limited, UK). PCT Int. Appl. (1999), 38 pp. CODEN: PIXXD2 WO 9937614 A1.

Azetidinecarboxamide derivatives for treating CNS disorders. Shepherd, Robin Gerald; Adams, David Reginald; Bentley, Jon; Bodkin, Corinna Dagmar; Cliffe, Ian Anthony; Davidson, James Edward Paul; Mansell, Howard Langham; Monck, Nathaniel Julius. (Cerebrus Limited, UK; Shepherd, Joy, Miriam). PCT Int. Appl. (1999), 46 pp. CODEN: PIXXD2 WO 9937613 A1.

Azetidinecarboxamide derivatives for treating CNS disorders. Shepherd, Robin Gerald; Adams, David Reginald; Bodkin, Corinna Dagmar; Cliffe, Ian Anthony; Mansell, Howard Langham; Monck, Nathaniel Julius. (Cerebrus Limited, UK; Shepherd, Joy Miriam). PCT Int. Appl. (1999), 35 pp. CODEN: PIXXD2 WO 9937612 A1 19990729.

Preparation of ortho-hydroxypyridinone derivatives as iron chelating and antioxidant agents. Bebbington, David; Monck, Nat; Gaur, Suneel; Palmer, Alan; Porter, Richard; Malcolm, Craig. (Cerebrus Limited, UK). PCT Int. Appl. (1999), 68 pp. CODEN: PIXXD2 WO 9923075 A1 19990514.

Studies Directed toward the Synthesis of the Unusual Antileukemic Diterpene Jatrophatrione. 2. Functionalization of Advanced Polycyclic Precursors to the 9-Epi and 8,9-Dehydro Congeners. Paquette, Leo A.; Edmondson, Scott D.; Monck, Nathaniel; Rogers, Robin D. Evans Chemical Laboratories, The Ohio State University, Columbus, OH, USA. J. Org. Chem. (1999), 64(9), 3255-3265.

Synthetic and structural studies on novel gibberellins. Pour, Milan; King, Geoffrey R.; Monck, Nathaniel J. T.; Morris, Jonathan C.; Zhang, Hongbin; Mander, Lewis N. Research School of

Chemistry, Inst. of Advanced Studies, Australian National Univ., Canberra, Australia. Pure Appl. Chem. (1998), 70(2), 351-354.

A New and Efficient Strategy for the Total Synthesis of Polycyclic Diterpenoids: The Preparation of Gibberellins (±)-GA103 and (±)-GA73. King, Geoffrey R.; Mander, Lewis N.; Monck, Nathaniel J. T.; Morris, Jonathan C.; Zhang, Hongbin. Research School of Chemistry, Australian National University, Canberra, Australia. J. Am. Chem. Soc. (1997), 119(16), 3828-3829.

Total synthesis of the spiroketal macrolide (+)-milbemycin α1. Ley, Steven V.; Madin, Andrew; Monck, Nathaniel J. T.. Univ. Chem. Lab., Cambridge, UK. Tetrahedron Lett. (1993), 34(46), 7479-82.